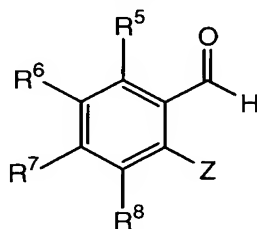


WHAT IS CLAIMED IS:

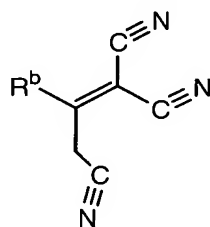
1. A method of making a tricyclic aminocyanopyridine MK-2 inhibiting compound, the method comprising:

reacting a substituted benzaldehyde having the structure:

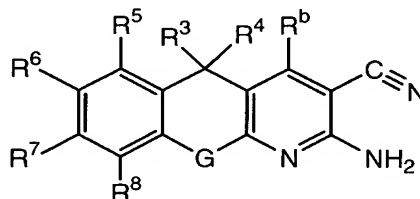


5

with a tricarbonitrile having the structure:



to form an aminocyanopyridine compound having the structure:



10

wherein:

Z is selected from the group consisting of -OH, -SH, and -NR^aY;

R_a is selected from the group consisting of alkyl, aryl, and heteroaryl;

15

Y is a protecting group for nitrogen that is selected from the group consisting of benzyl, allyl, alkyl carbamates and benzyl carbamate;

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, it is unsubstituted;

20

when G is sulfur, it is either unsubstituted or is substituted with one or two oxo groups;

when G is nitrogen, is it substituted with C₁-C₄ alkyl;

R^b is selected from the group consisting of furyl and -NH-R²;

5 R² is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

10 R³ and R⁴ are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties; and

15 R⁵, R⁶, R⁷ and R⁸ are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, halo, alkyl, alkenyl, alkyl, arylalkyl, alkylaryl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy, aminoalkoxy, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylamino, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, heterocyclylalkyl, heterocyclylalkoxy, carboxyalkoxy, alkylaminoalkoxy, alkylcarboxyalkoxy, pyrrolidylethoxy, hydroxyalkoxy, and alkylcarboxy, where R⁶ and R⁷ are such that they optionally join to form a six membered heterocyclic ring.

2. The method according to claim 1, wherein:

20 R² is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

25 R³ and R⁴ are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties;

R⁵ is selected from the group consisting of hydrogen, alkoxy, halo, alkyl, alkenyl, alkyl, arylalkyl, or alkylaryl;

30 R⁶ is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy, aminoalkoxy, halo, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylalkyl, alkylaryl, or arylamino;

R⁷ is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, heterocyclylalkyl, heterocyclylalkoxy, carboxyalkoxy, alkylaminoalkoxy, and alkylcarboxyalkoxy;

5 where the R⁶ and R⁷ groups can join to form a six membered heterocyclic ring; and

 R⁸ is selected from the group consisting of hydrogen, hydroxy, halo, nitro, amino, alkyl, alkoxy, heterocyclylalkoxy, carboxyalkoxy, pyrrolidylethoxy, carboxymethoxy, hydroxyalkoxy, aminoalkoxy,
10 alkylcarboxy, alkylaminoalkyl, carboxy, and heterocyclylalkyl.

3. The method according to claim 1, wherein the reacting step comprises heating the substituted benzaldehyde and the tricarbonitrile in a mixture of ethanol and acetic acid.

4. The method according to claim 3, wherein the mixture is
15 heated to reflux temperature at atmospheric pressure.

5. The method according to claim 4, further comprising recovering the aminocyanopyridine compound.

6. The method according to claim 5, wherein the recovering step comprises concentrating the reaction product of the substituted
20 benzaldehyde and the tricarbonitrile under vacuum; mixing the concentrated reaction product with trifluoroacetic acid; adding triethylsilane to the mixture of concentrated reaction product and trifluoroacetic acid; adding dichloromethane to the mixture of concentrated reaction product and trifluoroacetic acid; and collecting solids comprising the
25 aminocyanopyridine compound.

7. The method according to claim 6, wherein the triethylsilane is added to the concentrated reaction product while the mixture is being stirred at 0°C for about 1 hour.

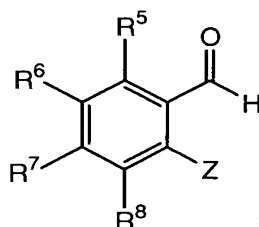
8. The method according to claim 6, wherein the solids are
30 collected by filtration and further comprising washing the solids with dichloromethane and ether.

9. The method according to claim 1, wherein the substituted benzaldehyde comprises salicaldehyde and the tricarbonitrile comprises 2-amino-1-propene-1,1,3-tricarbonitrile.

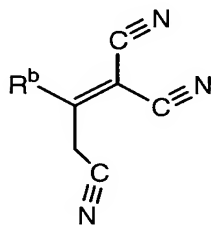
5 10. The method according to claim 1, wherein Y comprises tert-butylcarbamate.

11. A method of making a tricyclic aminocyanopyridine MK-2 inhibiting compound, the method comprising:

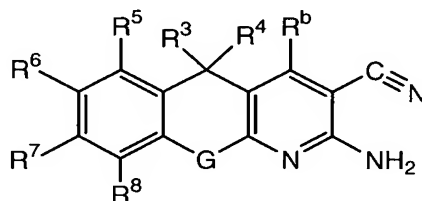
reacting a substituted benzaldehyde having the structure:



10 with a tricarbonitrile having the structure:



to form an aminocyanopyridine compound having the structure:



15 wherein:

Z is selected from the group consisting of -OH, -SH, and -NR^aY;

R_a is selected from the group consisting of alkyl, aryl, and heteroaryl;

20 Y is a protecting group for nitrogen that is selected from the group consisting of benzyl, allyl, alkyl carbamates and benzyl carbamate;

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, it is unsubstituted;

5 when G is sulfur, it is either unsubstituted or is substituted with one or two oxo groups;

when G is nitrogen, it is substituted with C₁-C₄ alkyl;

R^b is selected from the group consisting of furyl and -NH-R²;

10 R² is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

15 R³ and R⁴ are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties; and

R⁵, R⁶, R⁷ and R⁸ are each independently selected from the group consisting of:

hydrogen, hydroxy, amino, halo, nitro,

20 branched or unbranched C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, hydroxy C₁-C₆ alkyl, hydroxy C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, C₂-C₆ alkenoxy,

25 branched or unbranched amino C₁-C₆ alkyl, diamino C₂-C₆ alkyl, C₁-C₆ alkylamino C₁-C₆ alkyl, C₁-C₆ alkylamino, di-(C₁-C₆ alkyl)amino, C₁-C₄ alkoxyarylamino, C₁-C₄ alkoxyalkylamino, amino C₁-C₆ alkoxy, di-(C₁-C₄ alkylamino, C₂-C₆ alkoxy, di-(C₁-C₆ alkyl)amino C₁-C₆ alkyl, C₁-C₆ alkylamino C₁-C₆ alkoxy, halo C₁-C₆ alkoxy, dihalo C₁-C₆ alkoxy, trihalo C₁-C₆ alkoxy, cyano C₁-C₆ alkyl, dicyano C₁-C₆ alkyl, cyano C₁-C₆ alkoxy, dicyano C₁-C₆ alkoxy, carbamyl C₁-C₄ alkoxy, heterocyclyl C₁-C₄ alkoxy, heteroaryl C₁-C₄ alkoxy, sulfo, sulfamyl, C₁-C₄ alkylaminosulfonyl, hydroxy C₁-C₄ alkylaminosulfonyl, di-(C₁-C₄ alkyl)aminosulfonyl, C₁-C₄ alkylthio, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfinyl,

30

aryl, aryl C₁-C₆ alkyl, heterocyclyl C₁-C₆ alkyl, heteroaryl C₁-C₆ alkyl, heterocyclyl C₁-C₆ alkoxy, heteroaryl C₁-C₆ alkoxy, aryl C₁-C₆ alkoxy, where the aryl ring can be substituted or unsubstituted, and, if substituted, the substituent group is selected from one or more of the group consisting
5 of C₁-C₆ alkyl, halo, amino, and C₁-C₆ alkoxy,

substituted or unsubstituted C₃-C₆ cyclyl, C₃-C₆ heterocyclyl, and, if substituted, the substituent group is selected from one or more of the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, amino, and where the C₃-C₆ heterocyclyl ring contains O, S, or N,

10 branched or unbranched C₁-C₆ alkoxycarbonyl C₁-C₆ alkoxy, and carboxy, carboxy C₁-C₆ alkoxy, carboxy C₁-C₆ alkyl, hydroxy C₁-C₄ alkoxycarbonyl, C₁-C₄ alkoxycarbonyl.

12. The method according to claim 11, wherein:

R¹ is selected from the group consisting of hydrogen, branched or
15 unbranched alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, arylalkyl, carboxy, carboxyalkyl, hydroxyalkyl, alkylcarboxy, aryl, amino, aminoalkyl, alkylamino, halo, alkylaminoalkyl, alkoxy, alkoxyalkyl, monocyclyl, bicyclyl, polycyclyl, and heterocyclyl;

R² is selected from the group consisting of hydrogen, alkyl, alkenyl,
20 alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

R³ is selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where
25 substituents, if any, comprise halo moieties;

R⁴ is selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where
substituents, if any, comprise halo moieties;

R⁵ is selected from the group consisting of hydrogen, alkoxy, halo,
30 alkyl, alkenyl, alkyl, arylalkyl, or alkylaryl;

R⁶ is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, amino, alkylamino, arylamino,

alkylaminoalkyl, carboxy, aminoalkoxy, halo, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylalkyl, alkylaryl, or arylamino;

5 R^7 is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, heterocyclalkyl, heterocyclalkoxy, carboxyalkoxy, alkylaminoalkoxy, and alkylcarboxyalkoxy;

where the R^6 and R^7 groups can join to form a six membered heterocyclic ring;

10 R^8 is selected from the group consisting of hydrogen, hydroxy, halo, nitro, amino, alkyl, alkoxy, heterocyclalkoxy, carboxyalkoxy, pyrrolidylethoxy, carboxymethoxy, hydroxyalkoxy, aminoalkoxy, alkylcarboxy, alkylaminoalkyl, carboxy, and heterocyclalkyl; and

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

15 when G is oxygen, R^9 and R^{10} are absent;
when G is sulfur, each of R^9 and R^{10} is optionally absent or is oxo;
when G is nitrogen, R^9 is absent, and R^{10} is C₁-C₄-alkyl.

13. The method according to claim 11, wherein:

20 R^1 is selected from the group consisting of hydrogen, ethyl, dimethylaminoethyl, butyl, propyl, methoxyethyl, tetramethylaminoethyl, and carboxymethyl;

25 R^2 is selected from the group consisting of hydrogen, hydroxyethyl, propyl, ethyl, methyl, 4-methoxyphenyl, ethoxyethyl, aminoethyl, phenylmethyl, dimethylaminoethyl, phthaloaminoethyl, butyl, methoxyethyl, tetramethylaminoethyl, and carboxymethyl;

R^3 is selected from the group consisting of hydrogen, dicyanomethyl, 2-fluorophenyl, phenyl, and 3-fluorophenyl.

R^4 is selected from the group consisting of hydrogen, dicyanomethyl, 2-fluorophenyl, phenyl, and 3-fluorophenyl;

30 R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, bromo, and 2-pyridomethyl;

R⁶ is selected from the group consisting of hydrogen, hydroxy, methoxy, amino, carboxy, diaminoethoxy, bromo, propoxy, isobutylcarboxymethoxy, dimethylamino, nitro, phenyl, chloro, pyridylmethyl, and fluoro;

5 R⁷ is selected from the group consisting of hydrogen, hydroxy, methoxy, hydroxyethoxy, ethoxyethoxy, ethoxy, aminoethoxy, morpholinoethoxy, carboxymethoxy, *N*-pyrrolidylethoxy, dimethylaminoethoxy, pyridylmethyl, 2-propenoxy, and isobutylcarboxymethoxy, where the R⁶ and R⁷ groups can join to form a six
10 membered heterocyclic ring;

R⁸ is selected from the group consisting of hydrogen, hydroxy, fluoro, methoxy, nitro, amino, pyrrolidylethoxy, carboxymethoxy, methyl, hydroxyethoxy, aminoethoxy, 4-pyridylmethoxy, isobutyl, ethylcarboxy, dimethylaminoethoxy, carboxy, bromo, and pyridylmethyl; and

15 G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, R⁹ and R¹⁰ are absent;

when G is sulfur, each of R⁹ and R¹⁰ is optionally absent or is oxo;

when G is nitrogen, R⁹ is absent and R¹⁰ is -CH₃.

20 14. The method according to claim 11, wherein:

R¹ is selected from the group consisting of hydrogen, and C₁-C₂ alky;

25 R² is selected from the group consisting of hydrogen, C₁-C₃ alkyl, hydroxy C₁-C₂ alkyl, C₁-C₂ alkoxyphenyl, C₁-C₂ alkoxy C₁-C₂ alkyl, amino C₁-C₂ alkyl, phenyl C₁-C₂ alkyl, and di C₁-C₂ alkylamino C₁-C₂ alkyl;

R³ and R⁴ are each independently selected from the group consisting of hydrogen, dicyano C₁-C₂ alkyl, and halophenyl;

R⁵ is selected from the group consisting of hydrogen, and hydroxy;

30 R⁶ is selected from the group consisting of hydrogen, hydroxy, C₁ - C₃ alkoxy, amino, nitro, carboxy, diamino C₁ - C₂ alkoxy, halo, propenoxy, iso C₃ - C₄ alkylcarboxy C₁ - C₂ alkoxy, di C₁ - C₂ alkylamino, and phenyl;

R⁷ is selected from the group consisting of hydrogen, hydroxy, C₁ - C₃ alkoxy, hydroxy C₁ - C₂ alkoxy, C₁ - C₂ alkoxy C₁ - C₂ alkoxy, amino C₁ - C₂ alkoxy, morpholino C₁ - C₂ alkoxy, carboxyl C₁ - C₂ alkoxy, pyrrolidyl C₁ - C₂ alkoxy, di C₁ - C₂ alkylamino C₁ - C₂ alkoxy, pyrrolidyl C₁ - C₂ alkyl, iso C₃ - C₄ alkylcarboxy C₁ - C₂ alkoxy, and 2-propenoxy,

where the R⁶ and R⁷ groups can join to form a six membered heterocyclic ring;

R⁸ is selected from the group consisting of hydrogen, hydroxy, halo, C₁-C₂ alkyl, C₁-C₂ alkoxy, nitro, amino, pyrrolidyl C₁-C₂ alkoxy, carboxy C₁-C₂ alkoxy, hydroxy C₁-C₂ alkoxy, and amino C₁-C₂ alkoxy; and

G is selected from the group consisting of oxygen and sulfur;
when G is sulfur, each of R⁹ and R¹⁰ is optionally absent or is oxo;
when G is oxygen, R⁹ and R¹⁰ are absent.

15. The method according to claim 11, wherein:

R¹ is hydrogen;

R² is selected from the group consisting of hydrogen, C₁ - C₃ alkyl, hydroxy C₁ - C₂ alkyl, C₁ - C₂ alkoxyphenyl, C₁ - C₂ alkoxy C₁ - C₂ alkyl, amino C₁ - C₂ alkyl, phenyl C₁ - C₂ alkyl, and di C₁ - C₂ alkylamino C₁ - C₂ alkyl;

R³ and R⁴ are each independently selected from the group consisting of hydrogen, and dicyano C₁ - C₂ alkyl.

R⁵ is selected from the group consisting of hydrogen, and hydroxy;

R⁶ is selected from the group consisting of hydrogen, hydroxy, C₁-C₂ alkoxy, amino, carboxy, nitro, diamino C₁-C₂ alkoxy, halo, 2-propenoxy, iso C₃-C₄ alkylcarboxy C₁-C₂ alkoxy, di C₁-C₂ alkylamino, and phenyl;

R⁷ is selected from the group consisting of hydrogen, hydroxy, C₁ - C₂ alkoxy, hydroxy C₁-C₂ alkoxy, C₁-C₂ alkoxy C₁-C₂ alkoxy, amino C₁-C₂ alkoxy, morpholino C₁-C₂ alkoxy, carboxyl C₁-C₂ alkoxy, pyrrolidyl C₁-C₂ alkoxy, di C₁-C₂ alkylamino C₁-C₂ alkoxy, pyrrolidyl C₁-C₂ alkyl, iso C₃-C₄ alkylcarboxy C₁-C₂ alkoxy, and 2-propenoxy;

wherein the R⁶ and R⁷ groups can join to form a six membered heterocyclic ring;

R⁸ is selected from the group consisting of hydrogen, hydroxy, halo, C₁-C₂ alkoxy, nitro, amino, pyrrolidyl C₁-C₂ alkoxy, and carboxy C₁-C₂ alkoxy; and

G is selected from the group consisting of oxygen and sulfur;

5 when G is sulfur, each of R⁹ and R¹⁰ is optionally absent or is oxo;
when G is oxygen, R⁹ and R¹⁰ are absent.

16. The method according to claim 11, wherein:

R¹ is hydrogen;

10 R² is selected from the group consisting of hydrogen, C₁-C₃ alkyl,
hydroxy C₁-C₂ alkyl, C₁-C₂ alkoxyphenyl, C₁-C₂ alkoxy C₁-C₂ alkyl, amino
C₁-C₂ alkyl, and phenyl C₁-C₂ alkyl;

R³ and R⁴ are each independently selected from the group
consisting of hydrogen, and dicyano C₁-C₂ alkyl.

R⁵ is selected from the group consisting of hydrogen, and hydroxy;

15 R⁶ is selected from the group consisting of hydrogen, hydroxy, C₁-
C₂ alkoxy, amino, carboxy, diamino C₁-C₂ alkoxy, halo, 2-propenoxy, iso
C₃-C₄ alkylcarboxy C₁-C₂ alkoxy, and di C₁-C₂ alkylamino;

20 R⁷ is selected from the group consisting of hydrogen, hydroxy, C₁-
C₂ alkoxy, hydroxy C₁-C₂ alkoxy, C₁-C₂ alkoxy C₁-C₂ alkoxy, amino C₁-C₂
alkoxy, morpholino C₁-C₂ alkoxy, carboxyl C₁-C₂ alkoxy, pyrrolidyl C₁-C₂
alkoxy, di C₁-C₂ alkylamino C₁-C₂ alkoxy, pyrrolidyl C₁-C₂ alkyl, iso C₃-C₄
alkylcarboxy C₁-C₂ alkoxy, and 2-propenoxy;

where the R⁶ and R⁷ groups can join to form a six membered
heterocyclic ring;

25 R⁸ is selected from the group consisting of hydrogen, hydroxy, halo,
C₁-C₂ alkoxy, nitro, amino, and pyrrolidyl C₁-C₂ alkoxy; and

G is selected from the group consisting of oxygen and sulfur;

when G is sulfur, each of R⁹ and R¹⁰ is optionally absent or is oxo;

when G is oxygen, there R⁹ and R¹⁰ are absent.

30 17. The method according to claim 11, wherein:

R¹ is hydrogen;

R^2 is selected from the group consisting of hydrogen, C_1 - C_3 alkyl, hydroxy C_1 - C_2 alkyl, C_1 - C_2 alkoxyphenyl, C_1 - C_2 alkoxy C_1 - C_2 alkyl, and amino C_1 - C_2 alkyl;

5 R^3 and R^4 are each independently selected from the group consisting of hydrogen, and dicyanoethyl;

R^5 is selected from the group consisting of hydrogen, and hydroxy;

R^6 is selected from the group consisting of hydrogen, hydroxy, C_1 - C_2 alkoxy, amino, carboxy, diamino C_1 - C_2 alkoxy, halo, 2-propenoxy, iso C_3 - C_4 alkylcarboxy C_1 - C_2 alkoxy, and di C_1 - C_2 alkylamino;

10 R^7 is selected from the group consisting of hydrogen, hydroxy, C_1 - C_2 alkoxy, hydroxy C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_2 alkoxy, amino C_1 - C_2 alkoxy, morpholino C_1 - C_2 alkoxy, carboxyl C_1 - C_2 alkoxy, pyrrolidyl C_1 - C_2 alkoxy, di C_1 - C_2 alkylamino C_1 - C_2 alkoxy, pyrrolidyl C_1 - C_2 alkyl, iso C_3 - C_4 alkylcarboxy C_1 - C_2 alkoxy, and 2-propenoxy;

15 where the R^6 and R^7 groups can join to form a six membered heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, hydroxy, halo, methoxy, nitro, and amino; and

20 G is selected from the group consisting of oxygen and sulfur;
when G is sulfur, each of R^9 and R^{10} is optionally absent or is oxo;
when G is oxygen, R^9 and R^{10} are absent.